REMARKS

Entry of the foregoing and re-examination and reconsideration of the subject-application, as amended, pursuant to and consistent with 37 C.F.R. §1.112, and in the light of the Remarks which follow, are respectfully requested.

At the outset, Applicants note that they have canceled non-elected Claims 1-20, 24-29, 35, and 37-39.

By way of response, claims 21, 23, 30, 31, 33, 36, 40 and 50 have been amended, and claim 22 has been canceled and replaced by new claim 53. Some of the amendments are made, as discussed later, to correct the fact that some claims were dependent on canceled claims. Some amendments are made to insert SEQ ID Nos, and/or to clarify the claimed subject-matter. New claims 54 to 63 have been added. The support for these claims is set forth below. No new matter is presented. Claims 21, 23, 30 to 34, 36, and 40 to 53 are pending.

New claims 53 to 63 have been added. The support for these claims is as follows :

Claim 53 corresponds to the cancelled Claim 22.

The support for Claim 54 is at least at page 16, last paragraph, to page 17, first paragraph of the specification.

The support for Claim 55 can be found at least at page 17, first paragraph of the specification.

The support for claims 56 and 57 is at least in Example 8, at page 43, and in the former claims.

Claim 58 is supported at least by the specification at page 28 and at page 37, last paragraph.

The support for claims 59 to 61 is at least at page 28, paragraphs 2 and 3, and at page 37, last paragraph of the specification.

Support for Claim 62 can be found in the specification, at least at page 17, first paragraph.

The support for Claim 63 can be found at least in Example 8 at page 43, and at page 45.

Election / Restriction

Non-elected Claims 1-20, 24-29, 35, and 37-39 have been canceled without prejudice or disclaimer of the canceled subject-matter. Applicants reserve their rights to file a divisional application pertaining to the canceled subject-matter.

Oath / Declaration

Please find enclosed copy of the declaration in compliance with 37 CFR 1.67(a) that was filed on February 13, 1996, for the parent application. Applicants respectfully submit that the citizenship of each inventor is identified in this declaration.

Claim Objections

Claims 33 and 37 were objected to because they lacked a reference to a particular sequence identifier. Claim 33 has been amended to recite SEQ ID No: 12 or 13. Claim 37 has been canceled. Therefore, this rejection should now be rendered moot.

Claims Rejections – 35 U.S.C. § 112

Claims 21-23, 30-34, 36 and 40-52 were rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not provide enablement for a generic method that does not identify the specific disease state being detected, especially when using structurally uncharacterized probes that may or may not identify specific portions of undefined or unknown genes.

This rejection is partly obviated by the amendments made to claims 21, 30, 31, 33 and 36, and the replacement of claim 22 by new claim 53, and is partly being traversed.

Claims 21 and 53 have been amended and now pertain to kits for detecting a defect in the survival motor neuron gene (hereinafter referred to as SMN gene), comprising at least a set of defined primers hybridizing to the SMN gene (claim 21), or a defined probe hybridizing to the same gene (claim 53).

The support for this amendment is, for example; at page 39, third paragraph of the specification. In these claims, the term "defect" is to be understood as any alteration of the SMN gene, such as partial or total deletion, mutation, addition, or any other modification, as mentioned for example at page 6, paragraph 5 of the specification. Of course, one or several defect(s) can be detected according to the methods and using the kits of the invention.

Claim 23 pertains to a kit comprising a defined probe hybridizing to the SMN gene, for the detection of SMA.

Applicants respectfully submit that the specification does enable a person skilled in the art to make and/or use the invention commensurate in scope with these kit claims as amended. The rejection should hence be rendered moot for these claims.

Claim 30 as amended pertains to a method for detecting defects in the SMN gene, comprising an amplification step with primers hybridizing to the SMN gene.

The specification indicates which pair of primers can be used for the amplification of any specific part of the SMN gene. For example, primers of SEQ ID Nos: 5 and 6 are characteristic of exon 7 of the SMN gene, and primers of SEQ ID Nos: 7 and 8 are characteristic of exon 8 of the same, as indicated at least at page 12, lines 1 and 4 of the specification. At least pages 13 to 15 of the specification describe several pairs of primers that can be used for the amplification of each exon of the SMN gene. Lastly, it is clear from Figure 3 in the specification that the sequence comprising nucleotides 921 to 1469 of SEQ ID No: 12 corresponds to a non-coding sequence in exon 8.

Therefore, Applicants respectfully submit that the specification enables the skilled artisan to perform the method of claim 30 as amended.

Claims 31-34, 36, and 40-52 pertain to methods of the invention, which consist in analyzing the SMN gene of a patient, and deducing the patient's status having regard to a disease associated with said SMN gene.

Applicants respectfully submit that the specification enables the person skilled in the art to perform these methods. Indeed, the specification clearly identifies the wild-type SMN gene, referred to as T-BCD541, as explained, for example, at page 28, last line, and confirmed in the following pages. As noted at least at page 20, second paragraph of the specification, the entire SMN gene, including the introns and exons and devoid of the transcription regulating signals, is shown in Figure 10 (SEQ ID No: 21). The nucleotide sequence upstream of the coding region of the human SMN gene is also shown, in Figure 11 (SEQ ID No: 22) in the specification.

Besides, Applicants submit that the specification clearly demonstrates the correlation between alterations in the SMN gene and a variety of diseases such as Spinal Muscular Atrophy (see, for example, page 28: the T-BCD541 gene is lacking or truncated in 98% of 230 SMA patients in the disclosed study), and Arthrogryposis Multiplex Congenita (see, for example, pages 36 to 38).

The Examiner has cited an article by Rudinger that states that it is impossible to attach a unique significance to any residue in a sequence. However, Applicants submit that although a unique change in the amino acid sequence of the SMN protein does not necessarily lead to its misfunction, the knowledge that such a mutation exists can be an important point to do or confirm a diagnosis for a motor neuron disorder. Moreover, the clinical studies presented in the specification show that alterations of the SMN gene leading to SMN-related diseases are often either a complete lack or a truncation of this gene. This appears in the SMA study, which shows that the T-BCD541 gene is either lacking or truncated in 98% of 230 SMA patients, and in the study concerning AMC, in which 6 out of 12 patients lack the SMN gene.

As a conclusion, Applicants submit that it is clear from the specification that an alteration in the T-BCD541 gene is an important point to diagnose a spinal motor neuron disease, and that this point is even stronger when said alteration is a truncation or when the T-BCD541 gene is merely lacking.

From the above, Applicants respectfully submit that the specification does enable the skilled artisan to make and/or use the invention commensurate in scope with claims 21, 23, 30-34, 36, 40-52 and 53.

Withdrawal of this rejection is hence respectfully requested.

Claims 36 and 40 to 52 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly based on a disclosure which is not enabling because no

molecule containing the "T-BCD541 gene" or "SMN gene" has been deposited. This rejection is therefore respectfully traversed.

Applicants respectfully submit that the complete sequence of this gene is disclosed in Figure 10 (SEQ ID No: 21) of the specification, with all introns and exons. The nucleotide sequence situated upstream the coding region of the human SMN gene is also disclosed (Figure 11, SEQ ID No: 22). The disclosure of the complete nucleotide sequence of the SMN gene renders the deposit of a DNA molecule containing it unnecessary for enabling the skilled artisan to practice the invention.

Withdrawal of this rejection is therefore requested.

Claims 21 to 23 and 30 to 32 have been rejected under 35 U.S.C. § 112, second paragraph, because they were dependent on non-elected base claims. The amendments in claims 21 and 30, and the replacement of Claim 22 by new claim 53, render this rejection moot.

Claims 23, 30 to 32, 36, 40, 48 and 50 were rejected under USC 112, second paragraph, because of the abbreviations "SCCP" or "SMA". This rejection is obviated in part by amendment and traversed in part.

As noted, for example, at page 1, SMN means Survival Motor Neuron and SMA means Spinal Muscular Atrophy. It is respectfully submitted that "SCCP", in claim 36, is a typographical error. The exact abbreviation is "SSCP", for "Single-Strand Conformation Polymorphism", as shown for example at page 32 of the specification, last line. Claims 23, 30, 31, 36, 40 and 50 have been amended accordingly for clarification, hence rendering part of this rejection moot.

The Examiner has considered that the conditions for performing SSCP are not sufficiently described. This rejection is respectfully traversed. Indeed,

Applicants respectfully submit that the conditions for performing SSCP are described, for example, in Example 10, pages 44-45 of the specification.

From the above, withdrawal of the rejection is respectfully requested.

Claims 30 to 33 and 36 were rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential steps.

Claim 33 has been amended by adding step (d), "deducing the presence or absence of spinal muscular atrophy". Applicants respectfully submit that claims 30, 33 and 36 now recite all the essential steps of the claimed methods. Therefore, this rejection should be rendered moot.

Claims 33 and 34 have been rejected under 35 U.S.C. § 112, second paragraph, because the "stringent hybridization conditions" were allegedly not sufficiently defined. This rejection is respectfully traversed.

Applicants respectfully submit that the term "stringent hybridization conditions" is perfectly clear to the skilled artisan. The skilled artisan is able to determine the stringency of the hybridization conditions, which depend on the material used. Concerning the hybridization conditions, reference is made in the specification to Sambrook et al (at least at page 39, 1st paragraph). A copy of pages 9.47 to 9.51 of this book is enclosed herewith. These pages deal with the hybridization of radiolabeled probes to immobilized nucleic acids, and expose some generalities about hybridization conditions. Applicants respectfully draw the Examiner's attention to paragraph 9 of page 9.50, which teaches two things : first, that "*In general, the washing conditions should be as stringent as possible*", and the way to choose the temperature and salt concentration, and, second, that "*The temperature and salt conditions can often be determined in preliminary experiments in which samples of genomic DNA immobilized on filters are hybridized to the probe of interest and then washed under condition of different stringencies*".

In the method of Claim 33, appropriate conditions can be determined, for example, by using a control sample, i.e., a biological sample from an individual having a correct T-BCD541 gene. Applicants respectfully submit that this is part of the basic knowledge of the artisan skilled in the art at the time of filing of the present application, and that the hybridization condition do not need to be further defined in the claims to be understood.

Withdrawal of the rejection is hence requested.

Claims 21 to 23, 40, 43, 46 to 49 and 50 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the conditions for "an amplification reaction" or "analyzing exon 7" are not recited. This rejection is respectfully traversed.

Applicants respectfully submit that the phrase "amplification reaction" is perfectly clear to a skilled artisan. A variety of amplification reactions can be envisaged, such as Polymerase Chain Reaction (PCR) or Ligase Chain Reaction (LCR), for example. Concerning the phrase "analyzing exon 7", Applicants respectfully submit that the skilled artisan will also perfectly understand the meaning of the term "analyzing", having regard to the specification. Indeed, it is clear from the specification that the analysis of said exon can be performed by a variety of means, among which SSCP (as mentioned for example at page 16, last paragraph, in the specification), enzymatic restriction or sequencing (as mentioned at least at page 17, 1st paragraph). Alternatively, the analysis of exon 7 can be limited to the determination of whether this exon is present or not. From the above, Applicants respectfully submit that the subject-matter of claims 21, 23, 40, 46-49, 50 and 53 is clear to a skilled artisan.

Accordingly, withdrawal of the rejection is requested.

From the foregoing, favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $390.00 is attached hereto.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D. (Reg. No. 40,069) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachment: Version with Markings to Show Changes Made

MARKED-UP CLAIMS

21. (Once Amended) A kit for the *in vitro* detection of a defect in the survival motor neuron [diseases] gene, comprising:

[-] a set of primers [according to any one of Claims 15 or 16] wherein at least one of said primers is contained within the sequence of nucleotides 921 to 1469 of SEQ ID No: 12;

[-] reagents for an amplification reaction; and

[-] a probe for the detection of the amplified product.

23. (Twice Amended) [Kit] The kit [according to Claim 22] of Claim 53, for the detection of Spinal Muscular Atrophy (SMA).

30. (Once Amended) A method for detecting a defect in the Survival [m]Motor [n]Neuron gene [disorders including spinal muscular atrophy, any trophic lateral sclerosis and primary lateral sclerosis], said method comprising [the steps of]:

(a) extracting DNA from a patient sample;

(b) amplifying said DNA with primers [according to any one of Claims 15 or 16], wherein at least one of said primers is contained within the sequence of nucleotides 921 to 1469 of SEQ ID No: 12;

(c) subjecting said amplified DNA to a Single-Strand Conformation Polymorphism (SSCP); and

(d) [autoradiographing the gels; and

(e)]detecting the presence or absence of [the] said defect in the Survival [m]Motor [n]Neuron [disorder] gene, wherein the presence of said defect is indicative of a Survival Motor Neuron disorder.

31. (Once Amended) The method of Claim 30, wherein said detection of a defect in the Survival M[m]otor N[n]euron gene is indicative of a [disorder is] [s]Spinal [m]Muscular [a]Atrophy.

33. (Once Amended) A method for detecting [s]Spinal [m]Muscular [a]Atrophy, said method comprising [the steps of]:

(a) extracting DNA from a patient sample;

(b) hybridizing said DNA with a DNA probe comprising all or part of the DNA sequence of [Figure 3] SEQ ID Nos: 12 or 13 under stringent conditions ; [and]

(c) detecting the hybrids [possibly] formed; and

(d) detecting the presence or absence of Spinal Muscular Atrophy.

36. (Once Amended) A method for detecting [a]Arthrogryposis [m]Multiplex [c]Congenita (AMC), said method comprising [the steps of]:

(a) extracting DNA from a patient sample;

(b) amplifying said DNA via a polymerase chain reaction (PCR) using unlabeled primers from exon 7 [and] or exon 8 of the Survival Motor Neuron (SMN) gene of SEQ ID No:21;

(c) subjecting said amplified DNA to a Single Stranded Conformation Polymorphism (SSCP); and

(d) [autoradiographing the gels; and

(e)]detecting the presence or absence of [a]Arthrogryposis [m]Multiplex [c]Congenita.

40. (Once Amended) A method of detecting the presence in a human patient of an altered Survival Motor Neuron (SMN) gene associated with [s]Spinal [m]Muscular [a]Atrophy, comprising:

analyzing exon 7 or exon 8 of a gene identified as T-BCD541 (SEQ ID No: 21) in a biological sample derived from the patient, and

comparing said exon 7 or exon 8 to the corresponding exon [derived from T-BCD541 from normal human tissue] of SEQ ID No:13, which is present in a normal tissue;

wherein an alteration of either exon 7 or exon 8 in said patient sample with reference to said normal tissue is indicative of the presence of an altered Survival Motor Neuron (SMN) gene associated with [s]Spinal [m]Muscular [a]Atrophy in said patient.

50. (Once Amended) A method of confirming a clinical diagnosis of [a]Arthrogryposis [m]Multiplex [c]Congenita in a patient, comprising

analyzing exon 7 or exon 8 of a gene identified as T-BCD541 (SEQ ID No : 21) in a biological sample derived from the patient, and

comparing said exon 7 or exon 8 to the corresponding exon [derived from T-BCD541 from normal human tissue] of SEQ ID No:13, which is present in a normal tissue;

wherein an alteration of either exon 7 or exon 8 in said patient sample with reference to said normal tissue is indicative of the presence of an altered Survival Motor Neuron (SMN) gene associated with [a]Arthrogryposis [m]Multiplex [c]Congenita in said patient.

Please add the following claim :

53. (New) A kit for the *in vitro* detection of a defect in the survival motor neuron gene, wherein said kit comprises a probe which comprises at least 9 nucleotides within a sequence of SEQ ID No: 21 or hybridizes under stringent conditions with a sequence of SEQ ID Nos: 1, 2, 10-13, or 21.

54. (New) A method of identifying the presence or absence of a mutation in the Survival Motor Neuron (SMN) gene in a subject, comprising

(a) isolating a nucleic acid from the subject;

(b) subjecting the nucleic acid to digestion by a restriction endonuclease, wherein restriction fragments resulting from said digestion of a mutated SMN gene differ from those obtained from a T-BCD541 gene of SEQ ID No:21; and

(c) identifying the presence or absence of a mutation in the SMN gene in the subject.

55. (New) The method of claim 54, wherein the restriction endonuclease is *Bsr-1*.

56. (New) The method of claim 54, wherein the nucleic acid is further subjected to a polymerase chain reaction (PCR) following isolation.

57. (New) The method of claim 56, wherein said polymerase chain reaction is performed with a set of primers which are contained in the sequence comprising nucleotides 921 to 1469 of SEQ ID No: 12, or which comprise a sequence selected from SEQ ID Nos: 5 to 8 and 24 to 57.

58. (New) A method of identifying the presence of Spinal Muscular Atrophy (SMA) in a subject, said method comprising:

(a) isolating a nucleic acid from a subject; and

(b) identifying a mutation in a T-BCD541 gene (SEQ ID No: 21);

wherein the presence of a mutation in the T-BCD541 gene is indicative of the presence of SMA in said subject.

59. (New) The method of claim 58, wherein the mutation is a deletion in the T-BCD541 gene (SEQ ID No: 21).

60. (New) The method of claim 59, wherein the deletion comprises a deletion of the entire T-BCD541 gene (SEQ ID No: 21).

61. (New) The method of claim 59, wherein the mutation results in a truncation of the protein product encoded by SEQ ID No.: 12.

62. (New) The method of claim 58, wherein the sequence of the isolated nucleic acid is determined by direct sequencing.

63. (New) The method of claim 58, wherein the nucleic acid is further subjected to a polymerase chain reaction (PCR) following isolation.

64. (New) A kit for the *in vitro* detection of a defect in the survival motor neuron gene, comprising:

a set of primers wherein at least one of said primers comprises a sequence selected from SEQ ID Nos: 5 to 8 and 24 to 57;
reagents for an amplification reaction; and
a probe for the detection of the amplified product.

65. (New) A method for detecting a defect in the Survival Motor Neuron gene, said method comprising :

(a) extracting DNA from a patient sample;

(b) amplifying said DNA with primers, wherein at least one of said primers comprises a sequence selected from SEQ ID Nos: 5 to 8 and 24 to 57;

(c) subjecting said amplified DNA to a Single-Strand Conformation Polymorphism (SSCP); and

(d) detecting the presence or absence of said defect in the Survival Motor Neuron gene, wherein the presence of said defect is indicative of a Survival Motor Neuron disorder.